Chronic urticaria: Diagnosis and management

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ABSTRACT

Chronic urticaria (CU) is a common condition faced by the practicing allergist. There is a considerable degree of variation in the evaluation of patients with CU. The intent of this article is to provide the practicing allergist with an appropriate, evidence-based strategy for diagnosis and initial management of patients with CU. A review was performed of pertinent literature of CU pertaining to its natural history, impact on quality of life, subtypes, utility of diagnostic tests, and initial treatment recommendations. The reported duration of CU varies based on the nature of the referring center; however, physical urticarias persist longer than idiopathic CU. CU has adverse effects on quality of life and is comparable with other chronic diseases. Idiopathic urticaria, autoimmune CU, and physical urticarias are the most common types of CU. A detailed history is the best diagnostic tool in determining an etiology of CU and routine laboratory tests are of little value in the evaluation of CU patients. Antihistamines, particularly first-generation antihistamines, are the preferred initial treatment for CU and higher doses may be required for adequate control. Several alternative agents exist for patients who have antihistamine-resistant CU. A detailed history is the best tool for diagnosing the etiology of CU although most patients will not have a specific etiology found. The ultimate goal should be to control urticaria to reduce its impact on the quality of life of the patient, minimize adverse effects of medications, and eliminate chronic or frequent oral corticosteroids.

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Key words: Alternative agents, antihistamines, autoimmune, chronic urticaria, diagnosis, etiology, idiopathic, physical urticaria, tests, treatment

Chronic urticaria (CU) is a common condition faced by the practicing allergist. Many allergists are also reporting an increase in CU patients within their practices. This may be due to a number of reasons including reduction of referrals for other allergic diseases such as asthma and allergic rhinitis or decreased evaluations by dermatologists because of their gravitation toward cosmetic dermatology. The intent of this article is to provide the practicing allergist with an appropriate diagnostic and initial management strategy for patients with CU.

CLASSIFICATION

Urticaria has been arbitrarily classified primarily based on the duration of the urticarial episodes. Typically, urticarial episodes that last <6 weeks are considered acute urticaria. It has been estimated that 10–20% of the population may have an episode of acute urticaria at some point in their lives. Common causes of acute urticaria include IgE-mediated etiologies such as food allergy, drug allergy, and stinging insect reactions. In children viral infections are a common cause of acute urticaria. Nonetheless, in many patients with acute urticaria, an etiology may not be found.

CU has been defined as having urticarial episodes that last >6 weeks. Most patients have urticarial lesions daily or several days per week. Although a number of etiologies have been attributed to cause CU, the three most common etiologies are idiopathic, autoimmune, and physical urticarias. Some patients with recurrent urticarial episodes do not appear to fit exactly into the acute or chronic classification scheme. These patients may have episodes of urticaria that last <6 weeks but recur frequently. Whether these patients have recurrent acute urticaria or chronic intermittent urticaria is unclear, but my personal approach is to evaluate and manage them analogous to CU patients.

NATURAL HISTORY OF CU AND IMPACT ON QUALITY OF LIFE

One of the frequent questions patients with CU will ask is "How much longer will my hives last?"

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This is an important question to address with patients because many feel that once they develop urticaria it will never end, particularly if their urticaria has been ongoing for several months or years. Unfortunately, data on the natural history of CU are somewhat limited and based on the type of center, may not be applicable to the typical practicing allergist. A prospective study of 220 CU patients from a secondary-tertiary dermatology clinic in Amsterdam evaluated the spontaneous remission in patients followed for 1–3 years.[1] For patients with chronic idiopathic urticaria (CIU), 47% were free of symptoms after 1 year. In contrast, only 16% of patients with physical urticaria were free of symptoms after 1 year. A retrospective study of 372 CU patients from a "supra-regional referral center" in the Netherlands showed even lower rates of remission.[2] Only 29% of CU patients from this referral center were free of urticaria after 5 years, and even after 10 years, only 44% were in remission. Patients with physical urticarias and more severe disease had longer durations of CU. These studies and others indicate that patients with physical urticaria tend to have a longer duration of disease. I educate my patients with CIU that their condition may last several years but at some point will go away. For those with physical urticarias, I tell them their condition may be better measured in decades, rather than years. It is also important to indicate to CU patients that although their condition may last years, it can typically be controlled during that time and hence minimize the impact on their quality of life.

The detrimental impact of CU on quality of life is certainly obvious to most CU patients and allergists. However, the general population and most physicians view urticaria as nothing more than a minor nuisance. This may be because of the high frequency of the better known form of urticaria, acute urticaria, which because of its self-limited nature may propagate a false perception that CU is a trivial condition. Formal quality-of-life studies have been performed that may provide a sense of reassurance to CU patients (in that their condition is significant) as well as educate other physicians regarding the impact of this condition.[3] In a study of 170 CU patients from a specialty dermatology clinic, patients with CU had impairment of quality of life comparable with severe atopic dermatitis and worse than patients with psoriasis, Behcet's, and acne.[4] Another study from the same group evaluated 142 CU patients with a more general quality-of-life instrument and found impairment in CU patients to be similar to those reported in a previous study of patients awaiting coronary artery bypass surgery.[5]

Table 1 **Etiologies for acute and chronic urticaria**

Urticaria Etiologies	
Acute	**Chronic**
Foods	Idiopathic
Insect stings	Autoimmune
Viral infection	Physical
Contact	Cryopyrinopathies
Transfusion reactions	Urticarial vasculitis
Medications	Infections

ETIOLOGIES OF CU

Autoimmune Urticaria

Although numerous etiologies for CU exist, in the majority of cases, no cause can be found and hence a diagnosis of CIU is made. Nonetheless, it is important to consider specific etiologies in evaluating patients with CU (Table 1). A subset of patients with CU have evidence of autoantibodies, including autoantibodies to the high-affinity IgE receptor (FcεRI) and rarely anti-IgE antibodies. These patients may be classified as having autoimmune CU and have been previously discussed by Boguniewicz[6] and in other reviews.[7] Physical urticarias may often be distinguished by historical features of not only the triggering physical stimulus, but also the duration of the urticarial lesion itself. Individual physical urticaria lesions typically last between 30 minutes to 2 hours. In contrast, lesions of other types of CU, typically, last most of the day.

Physical Urticarias

Cold Urticaria. Cold urticaria represents 5–30% of physical urticarias, being more common in colder climates. Cold urticaria patients typically have urticaria on cold-exposed areas of the body. Systemic reactions including hypotension have been associated with outdoor swimming including reports of fatalities and therefore patients need to be educated about this risk.[8] Oropharyngeal edema on ingestion of cold substances has been reported to be a risk factor for shock-like reactions after swimming.[9] Cold urticaria is most often idiopathic but may also be associated with cold-dependent immunoglobulin diseases including cryoglobulinemia, cold agglutinin disease, cryofibrinogenemia, paroxysmal cold hemoglobinuria, and cold hemolysis. Cold urticaria is usually diagnosed using an "ice cube test," where an ice cube is placed on the arm for several minutes and is determined positive if an urticarial wheal develops on rewarming (Fig. 1). More severe cold urticaria is usually associated with briefer times of ice contact to induce urticaria. Uncommon causes of cold urticaria including autoimmune inflammatory syndromes, cold-induced cholinergic urticaria, sys-

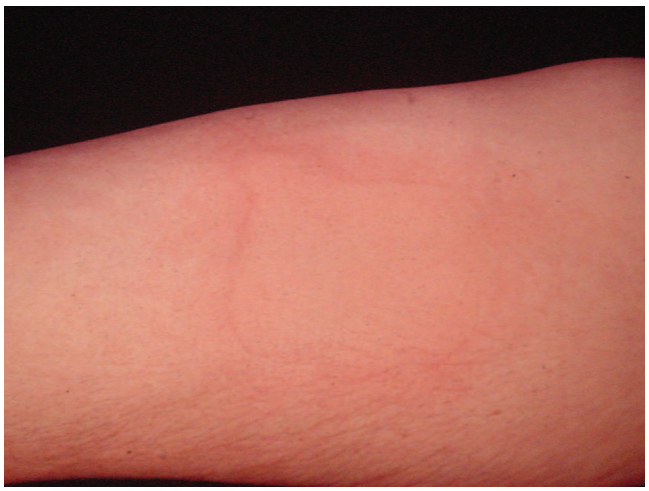

Figure 1. *Positive ice cube test as manifested by urticarial lesion on rewarming.*

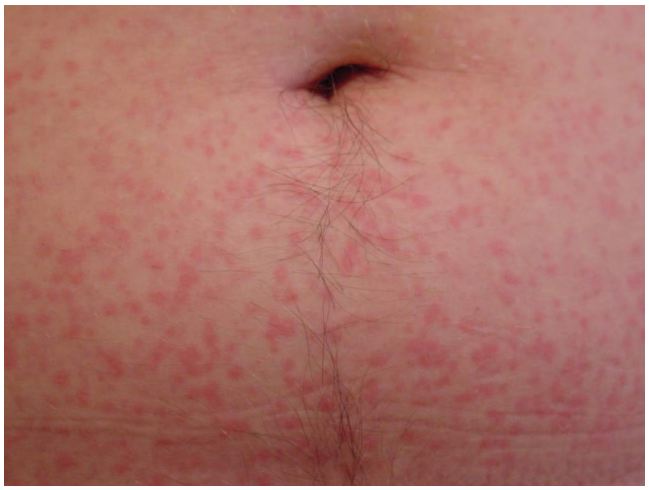

Figure 2. *Lesions of cholinergic urticaria.*

temic cold urticaria, and cold-dependent dermographism have negative ice cube tests.

Cholinergic Urticaria. Cholinergic urticaria represents ~30% of physical urticarias and 3–5% of CU. It occurs more often in teenagers and young adults. The lesions of cholinergic urticaria are unique in comparison with other forms of urticaria in that they are smaller (1–3 mm) and often macular initially (Fig. 2). They may be triggered by exercise, warm water, and emotional stress. In addition to urticaria, other cholinergic-mediated symptoms such as lacrimation, salivation, and diarrhea as well as wheezing may also occur. Recently, subgroups of cholinergic urticaria have been proposed based on the patient's response to autologous sweat testing.[10] Nonfollicular cholinergic urticaria is more common and patients have positive autologous sweat skin tests. Follicular cholinergic urticaria has weak to no response to autologous sweat skin tests but has positive autologous serum skin tests. Cholinergic urticaria can be diagnosed by exercise challenge or partial body immersion in hot water (44°C).

Delayed Pressure Urticaria (DPU). DPU represents ~2% of CU. Patients with DPU develop delayed cutaneous erythema and edema with often marked subcutaneous swelling after a pressure stimulus. When this swelling involves the hands or feet, it is indistinguishable from angioedema. Pressure-induced lesions typically occur 4–6 hours later, but may occur as early as 30 minutes and often last up to 48 hours. It is important to note that patients with DPU also have concomitant CIU and angioedema, and, hence, many of their lesions may not be exclusively be pressure related. Furthermore, many patients with CIU can have lesions that worsen at pressure sites (*e.g.*, beneath belts, and bra straps). The latter may explain some of the reports of high incidences of DPU in patients with CU. Historical features that aid in identifying patients with DPU include delayed urticarial lesions from shoulder straps; leaning against furniture; and wearing seat belts, tight clothing, and bra straps. Swelling of the feet may result from walking, jogging, or tight shoes. Swelling of the hands may result from carrying shopping bags or using a screw driver or hammer.

The most common method of testing for DPU is referred to as the "sand bag test." This test can be performed by using 15 lb of weight applied to the shoulder, thigh, or forearm for 15 minutes and observing the site over the next 24 hours for evidence of urticaria or edema. We typically use exercising weights of 7.5 lb attached to either end of a strap and apply this to the shoulder for 15 minutes and then the thigh for 15 minutes and have the patient observe these sites or take photographs. Unfortunately, this technique is not standardized and in my experience many patients with histories typical for DPU may have a negative test using this methodology. Other techniques including weighted metal rods or a calibrated dermographometer have also been used.[11]

Symptomatic Dermographism. Simple dermographism (dermatographia) is relatively common and occurs in 2–5% of the general population. Patients rarely seek out attention for this because the linear wheal and flare reactions that develop from stroking the skin are not pruritic. In contrast, patients with symptomatic dermographism (factitious urticaria and urticarial dermographism) have intense pruritus that often develops without a pressure stimulus but is certainly accentuated by minor stroking, rubbing, or scratching the skin. The lesions of dermographism are typically short-lived and last only 30 minutes. The incidence of symptomatic dermographism has not been well characterized. In our clinics, it is the most common type of physical urticaria. In a series of 40 patients from a dermatology

Table 2 **Testing for physical urticaria**

Physical Urticaria	Testing Method
Cold	Ice cube test
Localized heat	Test tube of water 44°C
Cholinergic	Exercise for 15–20 min Leg immersion in 44°C bath
Delayed pressure	Sand bag test: 15 lb weight for 15 min
Dermographism	Stroking skin firmly
Solar	Specific wavelength light exposure
Aquagenic	Water compress
Vibratory	Vortex for 4 min

clinic in Istanbul, psychic factors (*e.g.*, sudden changes in lifestyle or unexpected stressful life events) were found to have a triggering role in inciting dermographism in 30% of patients.[12] In addition, symptomatic dermographism also occurred in three patients after antibiotic-induced urticaria. Dermographism is easy to diagnose in the office by using a tongue blade to firmly stroke the skin and observe the area after 5 minutes for lesions. In our experience, the back may be a more sensitive area than the forearm in eliciting dermographism. A number of other physical urticarias exist but these are quite rare and include solar urticaria, aquagenic urticaria, and vibratory angioedema. Testing for the various types of physical urticarias is shown in Table 2.

Cryopyrinopathies. In the last several years, a number of well-known hereditary disorders have been linked together on the molecular basis of their cytokine dysregulation. Collectively, these disorders are referred to as autoinflammatory syndromes and include a number of hereditary periodic fever syndromes including familial Mediterranean fever, Hyper IgD syndrome, TNF receptor–associated periodic syndrome, and Blau syndrome. Another group of autoinflammatory syndromes is characterized by mutations in the same gene known as cold-induced autoinflammatory syndrome 1 gene (*CIAS1*). This gene encodes a protein called cryopyrin, a key component of the inflammasome complex, part of the innate immune system. Familial cold-autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disorder (NOMID) are all caused by *CIAS1* mutations and are collectively referred to as cryopyrinopathies.

FCAS, which used to be known as familial cold urticaria, is characterized by papular lesions on exposure to cold. These lesions are distinguished from typical urticaria because they are nonpruritic and often burning. In addition to cutaneous lesions, FCAS patients also have systemic symptoms including fever, chills, arthralgia, myalgias, and headache. The ice cube test is negative in patients with FCAS. Muckle-Wells syndrome may also have cutaneous lesions including cold urticaria and urticarial vasculitis, which is often present within the first few weeks of life. Hallmarks of this syndrome include deafness and renal amyloidosis. The most severe end of the spectrum of cryopyrinopathies is NOMID. In addition to an atypical urticarial rash, which begins early in life, patients have severe central nervous system manifestations including chronic aseptic meningitis, mental retardation, papilledema, cerebral atrophy, bony overgrowth, and amyloidosis. Treatment with the IL-1 receptor antagonist, anakinra, has recently been shown effective for NOMID and case reports indicate efficacy in other cryopyrinopathies.[13]

Urticarial Vasculitis (UV). UV may represent 5% of CU. It has a female predominance and has a peak incidence in the 4th decade of life. The clinical features of UV lesions are usually different from typical urticaria. UV lesions may be painful, tender, or have a burning quality and may be nonpruritic. The duration of individual UV lesions is typically longer in that they last between 24 to 72 hours when compared with nonvasculitic urticarial lesions, which typically last less than a day. However, large urticarial plaques may resolve over more than a day and this should not be confused with UV lesions. Having a patient circle a new lesion and monitoring how long it takes to disappear may be helpful in quantifying the duration of individual urticarial lesions. Another distinguishing feature of UV is that the lesions may resolve with purpura or hyperpigmentation. Angioedema can also occur in UV patients.

A number of systemic symptoms may be seen in UV including arthralgias, obstructive lung disease, uveitis, renal disease, and neurological problems. A more severe form of UV is associated with low complement and is referred to as hypocomplementemic UV syndrome (HUVS).[14] It typically has more frequent systemic symptoms including a higher frequency of obstructive lung disease.

Laboratory findings in HUVS include depressed C1q, C3, and C4 levels and low CH50. Anti-C1q antibodies and antinuclear antibodies may also be seen frequently in HUVS but in contrast to systemic lupus erythematosus (SLE), dsDNA is negative. Skin biopsy specimens are helpful in confirming UV but the histopathological changes may form a spectrum. Minimal criteria for diagnosing UV recommend leukocytoclasis or fibrin deposits in the lesions. UV is most commonly idiopathic but may be associated with SLE or Sjogren's

syndrome. There are several other reported causes and diseases associated with UV including infections, medications, paraproteinemias, hematologic diseases, complement deficiencies, physical urticaria, and malignancies that are beyond the scope of this article. Patients with UV are often refractory to antihistamines and numerous other agents have been used with variable efficacy.

Other Causes of CU. In the evaluation of patients with CU, allergists often consider a number of other associated diseases or conditions. Connective tissue diseases and, in particular, SLE are often listed in the differential of CU. However, most cases of urticaria in patients with SLE have UV when biopsied. Sjogren's syndrome is also associated with UV lesions. Cryoglobulinemia is a well-known complication of hepatitis C and usually presents with leukocytoclastic vasculitis. Therefore, in the absence of features suggestive of systemic disease or features of UV, evaluation for these connective tissue diseases in CU patients is not warranted. Other conditions such as *Helicobacter pylori* infection, candida infection, and malignancy are also considered in the evaluation of CU patients but there is minimal evidence for association with CU and therefore routine evaluation in the absence of a suggestive history is not recommended.[15] Food allergy, likewise, would be an extremely rare cause of CU and our current practice parameters state that food skin testing is inappropriate in the evaluation of patients with CU.[16] Viral infections are common causes of acute urticaria in children but may also exacerbate CU. Bacterial, fungal, and parasitic infections are rare causes of CU. The vast majority of CU patients in my clinic are idiopathic, which is the experience of most specialists.

DIAGNOSTIC TESTING IN CU

The most important diagnostic aid in evaluating patients with CU is a detailed history. Most physical urticarias can be suspected based on the history. UV similarly has many features that differentiate it from CIU. The cryoprinopathies are rare and their inheritance pattern and other clinical features easily separate them from CIU patients. Autoimmune urticaria can only be diagnosed by serological testing for autoantibodies or more specialized tests evaluating activation markers on basophils. However, the presence of autoantibodies to FcεRI has little predictive relevance to prognosis or treatment but may be helpful in stopping a patient from other fruitless searches for an etiology to their CU. A complete review of systems is essential in identifying any other systemic symptoms that would warrant a more directed laboratory evaluation.

In the absence of a suggestive history, which is most often the case, what diagnostic tests should be performed in the evaluation of patients with CU? This is the subject of debate and controversy among urticarial specialists. In clinical practice, there is a wide spectrum of evaluations ordered by practicing allergists ranging from no testing to extensive evaluations costing thousands of dollars. A systematic review of several studies addressing this issue helps to provide some recommendations based on the evidence. Kozel and colleagues performed a literature review on published series with >50 patients that evaluated diagnostic laboratories in CU.[17] They evaluated 29 studies involving 6462 patients. Overall, no relationship was found between the number of identified diagnoses and the number of laboratory tests performed. The range of identified diagnoses varied widely between studies as well as their causes. When evaluating those studies that excluded physical urticaria, the percentage of diagnoses was the lowest (1–20%). In only 1.6% of patients was an internal disease considered being the cause of CU; the majority of these (57%) were cutaneous vasculitis. Most authors concluded that history is very important (10 studies), that routine laboratory tests are of little value (13 studies), and that laboratory tests are only useful if based on the history (7 studies).

My opinion on diagnostic testing is similar to the results of the aforementioned review. In the absence of a suggestive history (including a complete review of systems), I do not perform any routine laboratory tests on CU patients. I question patients regarding any specific triggers they are concerned about at subsequent visits and can obtain appropriate testing as needed. If patients fail to respond to antihistamine therapy, I obtain laboratories for thyroid-stimulating hormone and thyroid autoantibodies. Although controversial, treatment with suppressive doses of thyroxine may be beneficial in patients with CU with thyroid autoantibodies.[18] In some patients, I do obtain autoantibodies to FcεRI, but this is primarily to help in concluding the workup of their CU. In patients I suspect have UV, complement levels, antinuclear antibody, and skin biopsy specimens are obtained, but I certainly do not advocate antinuclear antibody testing for all CU patients.

MANAGEMENT OF CU

Reassurance

One of the most important but often overlooked management strategies for CU patients is reassurance. Many patients referred to me from other specialists have not received the necessary reassurance and education on their disease and hence have a great deal of anxiety regarding their condition. Important messages for the patient include that CU is a relatively benign disease and even with associated angioedema is not a fatal condition. In this regard, I rarely prescribe self-

injectable epinephrine in CIU patients with angioedema because it tends to send the wrong message that their angioedema puts them at high risk for fatal laryngeal edema when in fact this is not the case. Nonetheless, there are those patients that feel safer having self-injectable epinephrine and in these cases a prescription may be reassuring. At the first visit I will instruct patients that although we rarely find a cause of CU, it has a self-limited course and, importantly, can usually be successfully managed in a way that will not significantly impair their quality of life.

Nonpharmacologic Therapies

Although many CU patients observe that certain nonspecific triggers aggravate their urticaria, it is important to discuss these with CU patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate urticaria in a significant percentage of CU patients and patients should be counseled on this possibility. Certainly, if patients require NSAID therapy and do not observe any flares in their CU, prohibition of these agents may not be necessary. Heat is another common trigger for CU patients as is tight clothing, the latter more of a problem for patients with DPU. Narcotics may also exacerbate some CU patients. Pseudoallergen-free diets are often recommended by European authorities but are rarely recommended in the United States. These diets are very difficult to adhere to but are easy to recommend, particularly if the patient is convinced that their CU is being caused by additives. In my experience, these diets are an effective way of disproving this belief in the occasional "additive-induced urticaria" steadfast believer.

Antihistamines in CU

Because nearly all symptoms of urticaria are primarily mediated by H_1-receptors located on nerves and endothelial cells, it is logical that H_1-antagonists are the mainstay of treatment for CU. Both first-generation and second-generation antihistamines have been used in the treatment of CU. A recent international consensus meeting on urticaria concluded that "considering their good safety profile, second-generation antihistamines must be considered as first line symptomatic treatment for urticaria."[19] They assessed data on second-generation antihistamines for urticaria as having a level of evidence of 1++ with a grade A recommendation. Studies comparing histamine-induced wheal suppression by H_1-antagonists generally show cetirizine and levocetirizine to have greater suppression of wheal formation compared with other second-generation antihistamines but studies showing the clinical correlation of this effect are lacking.[20] Comparative clinical data on second-generation antihistamines in CU show similar efficacy overall. Different individual responses to second-generation antihistamines are accepted as expert opinion.[19]

It is well recognized that many patients with CU may not respond to typically recommended doses of second-generation antihistamines and higher doses may be required. Studies evaluating cetirizine in doses ranging from 10 to 30 mg/day showed conflicting results with one study suggesting benefit from increased dosing[21] and another without demonstrable benefit.[22] The aforementioned international guidelines recommend using second-generation antihistamines at doses up to fourfold higher before considering alternative therapies but the level of evidence was low. In my experience, higher doses of second-generation antihistamines do improve some patients with CU but that increasing beyond twice the recommended dose is rarely beneficial.

First-generation antihistamines may also have a role in CU. Kaplan has been a proponent of using hydroxyzine, typically at doses of 50 mg four times daily and states that sedation is "variable and inconsistent" and "auto accidents have not occurred in those I treat, and no gross abnormality is discerned when interviewing or observing such patients."[23] Although sedation, lack of perception of sedation, and development of tolerance to sedation with first-generation antihistamines are well-known concepts, data in regards to CU patients are sorely lacking. I do prescribe hydroxyzine or doxepin in CU patients who have failed higher doses of second-generation antihistamines. However, I typically prescribe them as a single dose at bedtime and gradually increase the dose over time (in weekly increments) based on tolerance to sedation. In my experience, patients rarely derive added benefit from doses higher than 150 mg/day of either drug. Although sedation is certainly a problem, many patients can tolerate these drugs without adverse effects. I also recommend obtaining an electrocardiogram to monitor for QT prolongation in elderly subjects requiring >75 mg/day of first-generation antihistamines.

H_2-receptor antagonists have also been widely used for CU. The majority of studies evaluating the efficacy of these drugs in CU were with cimetidine. Cimetidine is an inhibitor of a number of cytochrome p 450 isoenzymes including those that are involved with metabolism of first-generation antihistamines. Plasma concentrations of hydroxyzine were higher in combination with cimetidine than with hydroxyzine alone.[24] This pharmacologic interaction may explain the perceived benefit of H_2-antagonists in CU. My own experience suggests that it is extremely rare for patients with CU to derive additional benefit from H_2-antagonists and that discontinuing them typically does not cause flares of CU.

Table 3 **Second-line alternative agents for refractory chronic urticaria**

Drug	Level of Evidence
Leukotriene modifiers	Ib
Dapsone	IIb
Sulfasalazine	III
Hydroxychloroquine	Ib
Colchicine	III
Calcineurin inhibitors	Ib
Mycophenolate	IIb
Omalizumab	III

Category of evidence[27]: Ia = evidence for meta-analysis of randomized controlled trials; Ib = evidence from at least one randomized controlled trial; IIa = evidence from at least one controlled study without randomization; IIb = evidence from at least one other type of quasi-experimental study; III = evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; IV = evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Alternative Agents for CU

Despite the use of antihistamines, some patients with CU remain refractory to this therapy. I define patients with antihistamine-resistant CU by having one of two features: (1) failure to control CU despite high doses of antihistamines or (2) patients intolerant of high-dose antihistamine therapy. Although, typically, systemic corticosteroids are used by many, this is not a recommended approach. Although systemic glucocorticoids are perceived to be effective in CU, interestingly, controlled data are lacking to establish their efficacy. More importantly, toxicity of systemic glucocorticoids is nearly inevitable in almost all patients treated for CU because doses requiring control are well above physiological doses.

A number of alternative agents are available to treat refractory CU. Some of the agents are immunomodulatory, some possess immunosuppressant activity, others have various anti-inflammatory effects, and many work through unclear mechanisms of action. A review of these alternative agents for CU is beyond the scope of this article but I would refer the reader to a two-part evidence-based review for more comprehensive information on this topic.[25,26] Table 3 lists the most reasonable alternative agents to consider for patients with refractory CU and their level of evidence.[27] The presence of autoantibodies to FcεRI does not have any consistent predictive effect of response to any alternative agent. For patients with antihistamine-resistant urticaria, I will typically start with medications such as leukotriene modifiers, dapsone, sulfasalazine, or hydroxychloroquine. For patients failing these alternative agents, calcineurin inhibitors are typically effective. I prefer tacrolimus because, in my experience, patients have less adverse effects compared with cyclosporine. Mycophenolate mofetil has even less adverse effects than calcineurin inhibitors but the published experience with this agent is currently less robust. Omalizumab may be another attractive option for allergists given their familiarity with this agent. Although the current evidence for omalizumab is limited to small case reports and series,[28] my own anecdotal experience has been very positive in an albeit small number of CU patients.

CONCLUSIONS

In summary, history is the best tool for diagnosing the etiology of CU. Most patients with CU will not have a specific etiology found (CIU). It is important to reassure patients about CU in relation to the prognosis of their condition, availability of efficacious treatments, and self-limited nature. Antihistamines are first-line therapy and effective in the majority of cases of CU. Nevertheless, some patients with CU are antihistamine resistant and may require alternative agents for adequate control of their CU. The ultimate goal should be to control urticaria to reduce its impact on the quality of life of the patient, minimize adverse effects of medications, and eliminate chronic or frequent oral corticosteroids.

REFERENCES

1. Kozel MM, Mekkes JR, Bossuyt PM, et al. Natural course of physical and chronic urticaria and angioedema in 220 patients. J Am Acad Dermatol 45:387–391, 2001.
2. van der Valk PG, Moret G, and Kiemeney LA. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. Br J Dermatol 146:110–113, 2002.
3. Weldon DR. Quality of life in patients with urticaria. Allergy Asthma Proc 27:96–99, 2006.
4. Poon E, Seed PT, Greaves MW, et al. The extent and nature of disability in different urticarial conditions. Br J Dermatol 140: 667–671, 1999.
5. O'Donnell BF, Lawlor F, Simpson J, et al. The impact of chronic urticaria on the quality of life. Br J Dermatol 136:197–201, 1997.
6. Boguniewicz M. Chronic urticaria: The autoimmune nature. Allergy Asthma Proc 2008.
7. Ozdemir O. Idiopathic (autoimmune) chronic urticaria. Allergy Asthma Proc 27:431–434, 2006.
8. Delore P, Gerin P, and Chapuy A. Drowning and urticaria caused by cold. J Med Lyon 37:497–503, 1956.
9. Mathelier-Fusade P, Aissaoui M, Bakhos D, et al. Clinical predictive factors of severity in cold urticaria. Arch Dermatol 134: 106–107, 1998.
10. Fukunaga A, Bito T, Tsuru K, et al. Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes. J Allergy Clin Immunol 116:397–402, 2005.
11. Lawlor F, and Black AK. Delayed pressure urticaria. Immunol Allergy Clin North Am 24:247–258, vi–vii, 2004.

12. Taskapan O, and Harmanyeri Y. Evaluation of patients with symptomatic dermographism. J Eur Acad Dermatol Venereol 20:58–62, 2006.
13. Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med 355:581–592, 2006.
14. Davis MD, and Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. Immunol Allergy Clin North Am 24:183–213, vi, 2004.
15. Kozel MM, and Sabroe RA. Chronic urticaria: Aetiology, management and current and future treatment options. Drugs 64: 2515–2536, 2004.
16. Bernstein I, Li J, Bernstein D, et al. Allergy diagnostic testing: An updated practice parameter. Ann Allergy Asthma Immunol 100:S1–S148, 2008.
17. Kozel MM, Bossuyt PM, Mekkes JR, et al. Laboratory tests and identified diagnoses in patients with physical and chronic urticaria and angioedema: A systematic review. J Am Acad Dermatol 48:409–416, 2003.
18. Gaig P, Garcia-Ortega P, Enrique E, et al. Successful treatment of chronic idiopathic urticaria associated with thyroid autoimmunity. J Investig Allergol Clin Immunol 10:342–345, 2000.
19. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: Management of urticaria. Allergy 61: 321–331, 2006.
20. Grant JA, Riethuisen JM, Moulaert B, et al. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: Suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. Ann Allergy Asthma Immunol 88:190–197, 2002.
21. Kameyoshi Y, Tanaka T, Mihara S, et al. Increasing the dose of cetirizine may lead to better control of chronic idiopathic urticaria: An open study of 21 patients. Br J Dermatol 157:803–804, 2007.
22. Asero R. Chronic unremitting urticaria: Is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed doses. Clin Exp Dermatol 32:34–38, 2007.
23. Kaplan AP. Chronic urticaria: Pathogenesis and treatment. J Allergy Clin Immunol 114:465–474, 2004.
24. Salo OP, Kauppinen K, and Mannisto PT. Cimetidine increases the plasma concentration of hydroxyzine. Acta Derm Venereol 66:349–350, 1986.
25. Morgan M, and Khan D. Therapeutic alternatives for chronic urticaria: An evidence-based review, part 1. Ann Allergy Asthma Immunol 100:403–412, 2008.
26. Morgan M, and Khan DA. Therapeutic alternatives for chronic urticaria: An evidence-based review, part 2. Ann Allergy Asthma Immunol 100:517–526, 2008.
27. Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: Developing guidelines. BMJ 318:593–596, 1999.
28. Spector SL, and Tan RA. Effect of omalizumab on patients with chronic urticaria. Ann Allergy Asthma Immunol 99:190–193, 2007. □